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**Expansion on stromal cells preserves the undifferentiated state of human hematopoietic stem cells despite compromised reconstitution ability.**

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**Public Summary:**

Shortage of suitable donors for blood forming stem cells (hematopoietic stem cells, HSC) limits the number of patients with life-threatening blood disorders that can be treated by HSC transplantation. So far, insufficient understanding of the regulatory mechanisms governing human HSC has precluded the development of effective protocols for culturing HSC for therapeutic use and molecular studies. We defined a culture system using OP9M2 stroma that protects human hematopoietic stem/progenitor cells (HSPC) from differentiation and cell death. In addition, it facilitates a dramatic expansion of multipotent hematopoietic cells that retain key properties characteristic of human HSC over several weeks in culture. In contrast, transplantable HSC could be maintained, but not significantly expanded, during 2-week culture. Temporal analysis of the genes expressed in the cultured hematopoietic cells documented remarkable stability of most transcriptional regulators known to govern the undifferentiated HSC state. Nevertheless, it revealed dynamic fluctuations in transcriptional programs that associate with HSC behavior and may compromise HSC function. This culture system serves now as a platform for modeling human multilineage hematopoietic stem/progenitor cell hierarchy and studying the complex regulation of HSC identity and function required for successful expansion of transplantable HSC for therapeutic purposes.

**Scientific Abstract:**

Lack of HLA-matched hematopoietic stem cells (HSC) limits the number of patients with life-threatening blood disorders that can be treated by HSC transplantation. So far, insufficient understanding of the regulatory mechanisms governing human HSC has precluded the development of effective protocols for culturing HSC for therapeutic use and molecular studies. We defined a culture system using OP9M2 mesenchymal stem cell (MSC) stroma that protects human hematopoietic stem/progenitor cells (HSPC) from differentiation and apoptosis. In addition, it facilitates a dramatic expansion of multipotent progenitors that retain the immunophenotype (CD34<sup>+</sup>CD38<sup>-</sup>CD90<sup>+</sup>) characteristic of human HSPC and proliferative potential over several weeks in culture. In contrast, transplantable HSC could be maintained, but not significantly expanded, during 2-week culture. Temporal analysis of the transcriptome of the ex vivo expanded CD34<sup>+</sup>CD38<sup>-</sup>CD90<sup>+</sup> cells documented remarkable stability of most transcriptional regulators known to govern the undifferentiated HSC state. Nevertheless, it revealed dynamic fluctuations in transcriptional programs that associate with HSC behavior and may compromise HSC function, such as dysregulation of PBX1 regulated genetic networks. This culture system serves now as a platform for modeling human multilineage hematopoietic stem/progenitor cell hierarchy and studying the complex regulation of HSC identity and function required for successful ex vivo expansion of transplantable HSC.

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